(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 462 957 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
24.04.2019 Bulletin 2019/17

(21) Application number: **11190599.8**

(22) Date of filing: **16.09.2004**

(51) Int Cl.:
A61L 24/08 *(2006.01)* ***A61L 24/00*** *(2006.01)*
A61K 31/19 *(2006.01)*

(54) **ABSORBABLE IMPLANTS AND METHODS FOR THEIR USE IN HEMOSTASIS AND IN THE TREATMENT OF OSSEOUS DEFECTS**

SAUGFÄHIGE IMPLANTATE UND VERFAHREN ZU IHRER VERWENDUNG BEI DER HÄMOSTASE UND DER BEHANDLUNG VON KNOCHENDEFEKTEN

IMPLANTS ABSORBABLES ET LEURS PROCEDES D'UTILISATION POUR UNE HEMOSTASE ET POUR TRAITER DES DEFAUTS OSSEUX

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR

(30) Priority: **23.09.2003 US 504978 P**

(43) Date of publication of application:
13.06.2012 Bulletin 2012/24

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
04781435.5 / 1 677 664

(73) Proprietor: **Abyrx, Inc.**
Irvington, NY 10533 (US)

(72) Inventor: **Kronenthal, Richard L.**
New Jersey 07410 (US)

(74) Representative: **Cooley (UK) LLP**
Dashwood
69 Old Broad Street
London EC2M 1QS (GB)

(56) References cited:
US-A- 4 439 420 **US-A- 4 568 536**
US-A- 5 681 873

EP 2 462 957 B1

Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0001] The invention relates to the management, treatment, therapy, and beneficial control of osseous conditions such as hemorrhage and defects, through the use of materials having various viscosities, cohesive strengths, and consistencies, most particularly putty-like materials as well as creams, pastes, ointments, lotions, and gels. More particularly, various novel, surgically implantable, absorbable formulations, which may contain absorption accelerants, bone growth-inducing materials, anti-infective or anti-neoplastic agents to reduce the risk of infection or tumor growth, respectively, analgesics, anti-inflammatory agents, clot-inducing agents such as vasoconstrictors and styptic materials, are used as bone hemostatic devices and/or as bone healing or therapeutic adjuvants. The compositions also may contain radiopaque materials and colorants.

DESCRIPTION OF RELATED ART

[0002] Cancellous and cortical bone contains relatively vascular tissues that bleed when their vasculature is disrupted. Thus, when bone is surgically incised or fractured traumatically, e.g., in open or compound fractures, there are at least two major issues which must be medically resolved. The first of these is the occurrence of osseous hemorrhage. When osseous hemorrhage ensues, it must be stopped or effectively controlled (hemostasis) to prevent adverse surgical consequences. The second issue is that of bone growth to promote healing (osteogenesis) of the traumatized bone. Common procedures in which bone is surgically cut include open-heart surgery involving the splitting of the sternum, orthopedic and spinal surgery including hip implants, neurosurgery involving spine or cranial incisions, amputations, trauma treatment, and many other procedures.

[0003] At the present time, bone hemostasis is achieved by one or more of (i) manually impregnating the bleeding surface with commercially available, non-absorbable "bone wax", (ii) the use of various hemostatic agents such as oxidized cellulose or microcrystalline collagen and (iii) electrocautery. None of these techniques promotes osteogenesis to any significant extent. In addition to the unmet need for an effective, rapidly absorbable bone hemostatic material, there is also a surgical need for materials to fill bone defect voids and promote healing in such cavities. A variety of paste-like materials, presently available to the surgeon for this purpose, most commonly are based upon coarsely powdered, demineralized allogeneic bone, suspended in a suitable, biocompatible vehicle. These compositions are designed for inducing osteogenesis and healing in the defect but, because of their consistency, non-cohesiveness and other physical attributes of their composition, they do not reliably adhere to injured bone and are not effective hemostatic agents.

[0004] There are two major bodies of prior art concerned with bone hemostasis and bone healing, respectively. As discussed below, up to the present time, in the main, only products based upon plasticized non-absorbable waxes have been available to the surgeon for bone hemostasis. The disadvantages of makeshift devices employing, for example, oxidized cellulose as well as the tissue-destructive use of electrocautery (discussed below) are not satisfactory alternatives.

[0005] The first body of art is directed specifically to bone waxes which are manually pressed into the pores of the bleeding bone surface, act as an effective mechanical tamponade, and prevent blood from escaping. Presently available bone waxes consist of mixtures of non-absorbable components such as bee's wax, paraffin, petrolatum, fatty ester plasticizers, and the like. These products must be warmed before use and become soft, kneadable and spreadable by the surgeon onto and into cut bone surfaces. Because available bone waxes are not absorbable and reside indefinitely where they are placed by the surgeon, they act as permanent physical barriers that inhibit osteogenesis, thereby preventing or slowing bone healing. In addition, such a site acts as a perpetual postoperative nidus for infection. If such infection does occur, it is usually chronic and difficult to treat using conventional anti-infective therapy and re-operation, to surgically excise the infected site, often becomes necessary. For these reasons, commercially available bone waxes do not enjoy widespread orthopedic use.

[0006] Other products or techniques used in this application include oxidized cellulose products indicated for soft tissue hemostasis, e.g., Surgicel®, which are absorbable and would not be expected to induce the complications cited above for bone wax. However, they are not effective hemostatic products for bone because of their inappropriate physical form (knitted fabric) and are too difficult to use effectively on cut bone because of lack of adherence within the bone pores.

[0007] The use of electrocautery, which thermally sears oozing blood vessels closed, is time-consuming and produces widespread tissue damage which may delay osteogenesis as well as allow soft tissue in-growth that interferes with normal bone union, presenting difficult problems for orthopedic surgeons in general and spine surgeons in particular.

[0008] Collagen in various forms, alone or in combination with fibrin and suspended in various delivery vehicles has been proposed as a bone hemostatic agent but problems with, for example, storage stability, cohesiveness, and biocompatibility have prevented practical fruition.

[0009] The adaptation of synthetic absorbable polymers to this application has not succeeded, apparently because of technical difficulties in suitably formulating hydrolytically unstable synthetic absorbable polymers into practical products with reasonable package shelf life,

useful handling properties and acceptable biocompatibility and absorption rates.

[0010] The second body of prior art primarily is concerned with bone healing and the treatment of bone defects. The bone healing prior art compilation primarily describes the development of biocompatible, absorbable vehicles to deliver and support processed particulate allogeneic bone as it is applied to defects such as excised cavities. These liquid or paste-like vehicles consist of a variety of polyhydroxy compounds, ester derivatives of polyols, hydrogels, and the like, sometimes containing additives to increase the viscosity of the vehicle (to retard dissipation of the vehicle and, thereby, extend the cohesiveness of the implanted mass) or factors to induce new bone growth. Anti-infective, anti-tumor and other additives also are described for these products. In no instances are these compositions indicated for, act as, or described in the art and claimed as bone hemostatic agents.

A. Bone Hemostasis

[0011] Attempts at providing absorbable bone hemostatic agents have not been completely successful. An absorbable bone sealant comprising fibrin and collagen (British Patent 1,584,080) requires mixing in the operating room. A reportedly hemostatic dispersion of microfibrillar collagen in polyethylene glycol (U.S. 6,117,444) loses coherence too rapidly as the glycol is dissipated. A microcrystalline collagen lyophilized sponge (U.S. 6,454,787), designed for soft tissue hemostasis, is not as well-suited for bone bleeding control. A hemostatic agent employing polylactide (U.S. 4,186,448), lactide/glycolide oligomers (U.S. 5,143,730, 6,420,454), moldable polymer blends (U.S. 5,641,502), absorbable, hydrogel-forming synthetics (U.S. 6,413,539) are not easily adapted to bone hemostasis. Polydioxanone (U.S. 4,443,430) synthetic absorbable polymer materials are difficult to employ because of their relative instability in biocompatible, protonic delivery vehicles. Another absorbable polyester such as a caprolactone polymer (U.S. 6,485,749) has been described as a replacement for bone wax.

[0012] A system with putty-like consistency at room temperature (U.S. 4,568,536), preferably combining a fatty acid salt, e.g., calcium stearate, an absorption enhancer, e.g., dextran and a vehicle, e.g., castor oil was developed as an absorbable, biocompatible matrix for the delivery of antibiotics, e.g., meclocycline sulfosalicylate, and other pharmacologically active agents to treat periodontal diseases. However, this technology, together with similar absorbable compositions described in U.S. 4,439,420 and U.S. 4,650,665, are deficient because they are designed for drug delivery over extended absorption time periods not thought optimal for rapid bone healing and because they contain dextran, a polysaccharide presently believed to be a toxicologically unacceptable implant material.

B. Bone Defect Healing

[0013] Materials designed for bone defect healing (but not hemostasis) are based upon pulverized cortical and/or cancellous allogeneic, demineralized, osteogenic bone powder, having particle sizes usually between 1 and 12 mm, in a biocompatible carrier selected from the group consisting of polyols, e.g., glycerol and polyol derivatives, e.g., glycerol monoacetate (U.S. 5,073,373, U.S. 5,484,601). Many additives are cited for this composition, e.g., anti-infective and anti-tumor agents, surfactants, vitamins, endocrine tissue, etc. A variant of this technology (U.S. 5,284,655) requires an increase of at least 10% in the volume of the demineralized bone component after contact with a swelling agent. The biocompatible suspending agent for the swollen demineralized bone particles is selected from the group including polyols and their esters, sucrose, polysaccharides, alginic acid, amylose, agar, etc. A further aspect of the 5,073,373 patent (U.S. 5,290,558) provides a flowable powder and claims large numbers of natural and synthetic polyhydroxy materials and their ester derivatives as vehicles for demineralized bone powder with a variety of additives such as BMP, IGF-1, anti-infective agents, hydroxyapatite, surfactants, bioerodable polymers and a variety of thickening agents such as PVA, PVP, CMC, gelatin, dextran, collagen, polyacrylate salts, etc. To improve handling characteristics of bone defect fillers (U.S. 5,314,476), particularly implant adhesion after the suspending vehicle is dissipated, demineralized bone particles of relatively high (10:1) median length to median thickness ratios are suspended in vehicles cited in the '558 patent. In an entirely different approach (U.S. 6,030,635), powdered demineralized bone carriers, based upon aqueous solutions of polyelectrolytes such as sodium hyaluronate, chitosan and N,O-carboxymethyl chitosan, are claimed. These viscous, high molecular weight hydrogels may contain anti-infective and other additives. A variant of U.S. Patent No. 6,030,635 (U.S. 6,437,018) includes the addition of a sodium phosphate buffer to form a more viscous hydrogel carrier for smaller particle sizes of mineralized or demineralized bone.

[0014] A recently issued patent (U.S. 6,565,884) describes a composition based on suspended demineralized bone matrix in lecithin or in lecithin containing unsaturated triglycerides, e.g. corn oil. The product is said to induce bone growth. However, it is probable that the surface-active composition may easily be washed away after. implantation. In yet another attempt to provide a useful material to stimulate new bone formation (U.S. 6,576,249), methods are described in which demineralized bone matrix is dissolved in water to form a viscous solution to which is added mineralized or demineralized bone matrix particles that form a water soluble, gel-like suspension.

[0015] As mentioned previously, in a search for a system to act as a matrix for the controlled delivery of various drugs, primarily for the treatment of periodontal diseases,

workers developed absorbable, biocompatible, putty-like compositions that adhered to bone (teeth), were conformable at room temperature and easily applied (U.S. 4,568,536). While the primary objective of this composition was for prolonged drug delivery, the system was based largely upon earlier disclosed putty-like compositions specifically developed as bone hemostatic agents (U.S. 4,439,420).

[0016] The compositions described in U.S. 4,439,420 are based essentially upon combinations of three types of materials, a fatty acid salt, preferably calcium stearate, a fluid base, preferably castor oil, and an absorption accelerator, preferably dextran. This preferred composition, when tested for absorbability as an intramuscular implant, was described as taking approximately four weeks to absorb. No information or data concerning efficacy as a hemostatic device were presented and apparently no experiments were done to determine the absorption rate of the material when actually used as a bone hemostatic device. Absorption from the enclosed interstices of bone trabeculae would be expected to be significantly slower than absorption from the more anatomically "open" intramuscular site used as a model.

[0017] The 4,439,420 patent discloses alternatives for the three preferred ingredients. Alternatives to calcium stearate are magnesium, zinc, aluminum, lithium and barium salts of saturated and unsaturated fatty acids containing from 10 to 22 carbon atoms (collectively, fatty acid salts). Alternatives to castor oil are ethylene oxide/propylene oxide block copolymers, polyethylene glycols, methoxy polyethylene glycols, triglycerides, fatty acid esters, sesame oil, almond oil, cottonseed oil, corn oil, olive oil, cod liver oil, safflower oil and soya oil (collectively molecules which, admixed with the fatty acid salt, form the slowly absorbable putty-like mass). Alternatives to dextran are Carbowax®, the Pluronics®, glycerine and propylene glycol, which act as absorption accelerators by post-operatively absorbing fluids and/or dissipating, thereby physically disrupting the implant mass as it resides in tissue.

[0018] The primary reasons the 4,439,420 putty-like compositions are unsuited for bone hemostasis are that the material, while eventually biodegradable, is absorbed too slowly and, thus, inhibits new bone growth infiltration and healing by acting as a physical barrier, much as do the nonabsorbable, paraffin-based bone waxes. In addition, the preferred composition described in the patent contains a component, i.e., dextran, which is not acceptable toxicologically. Finally, 4,439,420 compositions are "completely free of fibrous materials" which may be a significant disadvantage for optimum osteogenesis, a desirable characteristic for a bone hemostatic device. The addition of agents such as demineralized bone, bone growth factors and fibrous collagen to enhance osteogenesis and healing and anti-infectives to inhibit infection are not disclosed in the 4,439,420 patent.

BRIEF SUMMARY OF THE INVENTION

[0019] The formulations of the present invention are compositions having various viscosities and cohesive strengths and include putty and non-putty formulation consistencies.

[0020] The term "putty" is used herein as it is used in the art and is generally known to the skilled artisan. Dough (such as pastry dough), modeling clay, and glazier's putty of varying viscosities, depending on the indications and ultimate use, are examples of the consistency of a suitable product. Putties of various viscosities useable in the invention include those that are capable of adhering to bone. In general, putties which are soft, moldable, preferably non-elastic, cohesive mixtures prepared from a finely powdered substance intimately admixed with a liquid dispersing vehicle and having a shape which is capable of being deformed in any direction, are suitable consistencies for the putty-like compositions of the invention. As will be described later, however, compositions which have lower cohesive strengths than the putties described above, are within the scope of the invention, and may be used in specific applications in which the more viscous, higher cohesive strength putties are less suitable. For purposes of this invention, a major difference between putties of the invention and materials not considered to be putties (i.e. non-putties), but which are still within the scope of the invention, is that the non-putties have lower cohesive strengths than the cohesive strengths of the putty formulations. Individual non-putties of the invention are characterized by having the cohesive strength of creams, pastes, ointments, lotions, foams, gels, whipped egg whites, whipped cream, and the like. Preferably, the non-putties have only a fraction of the cohesive strength of putties of the invention, tending to be easily collapsible or easily torn apart under small stresses that would not, generally speaking, have the same effect on putties. The description, which follows is given mainly in the context of the putties of the invention, it being understood, however, that if less cohesive strength materials are desired, the skilled artisan will simply make the appropriate changes in the proportions of components or add other substances to achieve the same purpose.

[0021] The present invention involves formation of medically useful absorbable putty-like and non-putty-like compositions using dispersing vehicles not previously reported for preparing such materials, intimately admixed with finely powdered bulking agents, some of which have been previously used, but not with the present dispersing vehicles, and some of which have not heretofore been used, in preparing such putty-like and non-putty-like compositions.

[0022] A sterile, absorbable bone hemostatic agent, that is, a material that will provide virtually immediate surgical hemostasis and also will absorb in the body after a relatively short period of time without compromising hemostasis efficacy, would have significant medical ad-

vantages over presently available materials. It would minimally inhibit osteogenesis and subsequent bone healing. Moreover, bone-healing adjuvants such as growth factors, particularly, for example, platelet derived growth factor (PDGF) and/or bone morphogenic proteins (BMPs) and others, could be added to the formulations to stimulate the bone healing process. Furthermore, adding agents such as collagen, demineralized bone matrix (DBM), and/or hydroxyapatite could make the hemostatic material beneficially osteoconductive and osteoinductive. The addition of a suitable anti-infective agent such as antibiotics typified by tobramycin and gentamicin or bacteriostatic and bacteriocidal materials such as iodine, silver salts, colloidal silver, or the like serve to reduce the potential for infection, particularly in contaminated open wounds such as compound fractures. The addition of colorants would aid in visibility during the operative procedure. The addition of radiopaque substances allows the observation of post-operative sequelae using radiography. The addition of chemotherapeutic agents or radionuclides is useful when the putty is used, for example, in bone cavities arising from tumor resection. Analgesic compounds to reduce pain, and vasoconstrictors and blood clot-inducing agents to reduce hemorrhage, are useful additives.

[0023] The novel and inventive concepts described below for the preparation of the products of the present invention include at least two components, Component 1 being a bulking agent and Component 2 being a dispersing vehicle which, when intimately admixed with the bulking agent in appropriate proportions, yields a base for products of the invention. The selection of a suitable Component 2 will result in a composition that is absorbed by the body within an acceptable period of time. In such a case, Component 2 will act as its own absorption accelerant and the formulation will not require a separate absorption accelerant. If desired, however, the composition of the invention also may be provided with an optional ingredient which serves to accelerate the absorption of the putty by the body.

[0024] The invention provides implantable, appropriately absorbable, biocompatible, putty-like compositions that are useful as mechanical hemostatic tamponades for the control of osseous hemorrhage arising from surgical intervention or trauma and for providing an osteoinductive matrix to foster improved bone healing.

[0025] The scope of this invention is defined by the claims. Any references in the description to methods of treatment refer to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy (or for diagnosis).

[0026] Accordingly, one aspect of the invention provides sterilizable putty-like compositions of matter and methods for their use comprising the step of physically pressing the putty-lilce compositions into the bleeding area of bone, thus mechanically staunching bleeding, after which the composition is absorbed and harmlessly eliminated from the body.

[0027] In another aspect, particularly useful in, but not necessarily limited to, traumatically opened wounds, an anti-infective agent is added to, and then post-operatively released from, the putty-like composition to inhibit the occurrence of postoperative infection.

[0028] In another aspect, the invention provides for adding to the art-known non-absorbable or slowly absorbable bone hemostatic materials, one or more of mineralized or demineralized bone particles, collagen, hydroxyapatite, bone morphogenic protein and/or other bone growth factors to form a novel putty-like composition for the dual purpose of providing initial hemostasis and then stimulating new bone formation.

[0029] In another aspect, the invention provides for the addition of an anti-infective agent to the putty-like composition containing bone growth stimulating additives to inhibit the occurrence of postoperative infection.

[0030] The anti-infective agent, which may be an antibiotic, a bacteriostatic or a bacteriocidal material, may be added to the putty-like mass or may be reversibly bound to additives, e.g. gelatin or collagen, which are to be contained within the putty. For example, using iodine as the anti-infective agent, a complex of iodine with gelatin, collagen or PVP may be used. In addition, colloidal silver, silver salts, or silver complexes with gelatin or other polymers may be used. Still further, antibiotics, in addition to being capable of being added to the putty as described above, may be added as part of a delivery system, preferably as part of a component of the putty. In particular, gentamicin, bound to powdered collagen, is an example of a useful antibiotic release system. Similarly, anti-neoplastic agents may be added to the putty-like composition in the same manner, preferably as a free agent, to provide an effective anti-tumorigenic material. Analgesics to reduce pain, blood clot-inducing agents to act as chemical hemostatic agents, and anti-inflammatory agents, may also be added. Furthermore, radiopaque components may be added to allow radiographic observation and colorants to improve intra-operative performance.

[0031] Additional objects, features and advantages will be apparent in the written description that follows.

DETAILED DESCRIPTION OF THE INVENTION

[0032] The compositions of the present invention include compositions comprising at least two and preferably three, four, or more components. They are body absorbable. In many embodiments they have a putty-like consistency. In one embodiment, the compositions are mechanically hemostatic tamponades useful in stopping the bleeding of bone by the application of the putty-like composition to the affected area. By "mechanically hemostatic tamponades" is meant that the compositions function by mechanically compressing the bleeding areas of the bone to arrest hemorrhaging as opposed to functioning by chemically hemostatic means, i.e. the arresting of hemorrhaging, in whole or in part, using a

chemical means. In another embodiment, the compositions, in addition to being mechanically hemostatic, are also osteogenic in that they contain an added ingredient, i.e. a bone growth-inducing material, to aid in the induction of bone growth. Of the at least two components mentioned in the first sentence of this paragraph, Component 1 is a finely powdered bulking material having an average particle size sufficiently small to form a putty-like consistency when intimately admixed with the second component, i.e. dispersing vehicle Component 2 of the invention. More specifically, Component 1 is a finely powdered carboxylic acid salt comprising a carboxylate anion and a metallic cation, wherein said carboxylic acid is carboxymethyl cellulose and wherein the average particle size of component 1 is 50 microns or less. The Component 2 dispersing vehicle is a liquid which, when intimately admixed with Component 1, enables the formation of the putty-like implant. More specifically, Component 2 is a liquid comprising a member selected from the group consisting of polyhydroxy cmopounds, polyhydroxy compound esters and polyhydroxy compound ethers, and mixtures of the foregoing. While the two-component compositions of the invention provide the basic characteristics of suitable hemostatic materials as described herein, they may also, but are not required to, contain, if desired, optional ingredients 3 through 12, shown below. For example, optional Component 3 is an absorption accelerator, and Optional Component 4 is a bone growth-inducing material. Other components may be added to provide additional attributes to the putty-like and non-putty like compositions of the present invention as will be explained in more detail below.

[0033] Following is a detailed description of the various components.

Component 1

[0034] Component 1 is comprised of a finely powdered, preferably micronized, biocompatible, body-absorbable substance which, when admixed with a liquid dispersing vehicle, Component 2, forms the compositions of the invention. Suitable compositions are obtained when the average particle sizes of Component 1 materials are 50 microns or less, but the preferred average particle size range is between about 3 to about 25 microns and most preferably about 6 to about 15 microns especially when putty-like compositions are desired. Particle sizes for non-putty compositions may range higher than those of the putty compositions, if desired.

[0035] Component 1 is a finely powdered carboxylic acid salt comprising a carboxylate anion and a metallic cation. Carboxymethyl cellulose is the carboxylic acid. Suitably, the salts may be the calcium, magnesium, zinc, aluminum, lithium or barium salts.

[0036] This novel approach, discussed above, i.e., forming useful absorbable putties by drastically reducing the particle size of the bulking vehicle Component 1, overcomes many of the difficulties of the prior art, especially those of synthetic absorbable polymers as bone hemostatic agents.

Component 2

[0037] As the second component, i.e., the material which is mixed with Component 1 to obtain the composition of the invention, there may be mentioned several classes of materials that have not been heretofore employed as dispersing vehicles for preparing medical putties. At the outset, it should be noted that Component 2 is biocompatible and a liquid because the liquid form facilitates the admixture with Component 1 to form the putty or non-putty mass. More specifically, Component 2 is a liquid comprising a member selected from the group consisting of polyhydroxy compounds, polyhydroxy compound esters and polyhydroxy compound ethers, and mixtures of the foregoing.

[0038] To aid in understanding the terms used herein and to help differentiate this aspect of the invention from that of the prior art, it would, perhaps, at this point, be useful to emphasize the nature of the chemical entities referred to in this Specification by briefly reviewing relevant classical chemistry terminology to ensure the appropriate chemical distinctions are understood.

[0039] Carboxylic acids are substances defined by the attachment of an OH group to a carbonyl function through a covalent bond. As a result, carboxylic acids possess physical and chemical properties totally distinct from substances containing either the carbonyl functionality (e.g., aldehydes, ketones) or the hydroxyl functionality (alcohols). The same distinction holds true for substances containing both the carbonyl and hydroxyl groups not directly attached through a covalent bond, such as hydroxyacetone, which displays both ketone and alcohol properties, but not carboxylic acid characteristics. Carboxylic acids always combine a carbonyl and an OH group and have acidic characteristics, but the OH group does not have the characteristics of the hydroxyl group of an alcohol. A monocarboxylic acid would, therefore, not be described as a monohydroxy compound. To illustrate this, consider acetic acid and ethanol which are both two-carbon compounds containing an OH group. In acetic acid, the hydrogen atom of the OH group is liberated as an ion in water, whereas in ethanol, the hydrogen atom of the hydroxyl group is not so liberated. Thus, carboxylic acids dissociate and form carboxylate salts with bases, e.g., calcium stearate, a distinctive property that clearly differentiates the OH group of carboxylic acids from the hydroxyl group of alcohols that do not dissociate to form salts with bases. Thus, it would be entirely incorrect to characterize a carboxylic acid as an alcohol, a monohydric alcohol, or some such term since it is, in no chemical sense, an alcohol. Nor could a polycarboxylic acid be referred to as a polyalcohol, or a polyhydroxy compound or a polyol simply because it contains carboxylic OH groups. Such groups are not characterized as alcohols. An example of these distinctions is illustrated by consid-

ering the well-known molecule, citric acid. This substance has three carboxylic groups and one hydroxyl group in the same molecule. Citric acid is a monohydroxy (monohydric) alcohol as well as a polycarboxylic acid. The fact that citric acid contains three carboxylic OH groups does not classify this monohydroxy compound as a polyhydroxy compound. Because of the major differences in reactivity, synthesis and reactions, in every textbook of organic chemistry, the chemistry of alcohols always is considered in a separate chapter from the chemistry of carboxylic acids.

[0040] Alcohols may be regarded either as hydroxyl derivatives of hydrocarbons or as alkyl derivatives of water. They are typified by the R-OH structure where R is an alkyl group. In contradistinction to the readily ionizable hydrogen atom of the carboxylic acid hydroxyl group, the R-OH hydrogen atom is virtually unionized in water. On this basis, aliphatic alcohols are considered neutral rather than acidic. One or more hydroxyl groups may be appended to a hydrocarbon moiety so that, for example, propane may have one hydroxyl group (propyl alcohol), two hydroxyl groups (propanediol or propylene glycol) or three hydroxyl groups (propanetriol or glycerol). Propylene glycol and glycerol are simple examples of polyols. Polysaccharides, such as hyaluronic acid, contain many hydroxyl groups on each monomer unit and are correctly termed polyols. Alcohols may have short alkyl chains such as methyl alcohol, ethyl alcohol, propyl alcohol, etc., or they may have longer alkyl chains such as lauryl alcohol, myristyl alcohol, etc. It is of critical importance to note that lauric acid ($C_{11}H_{23}COOH$, a fatty acid) and lauryl alcohol ($C_{12}H_{25}OH$, a fatty alcohol) are completely different molecules in oxidation state and functionality, even though they both contain twelve carbon atoms.

[0041] Esters are commonly derived from the reaction of a carboxylic acid with an alcohol and can be converted back to the original carboxylic acid and alcohol by hydrolysis. Thus, acetic acid and ethyl alcohol are combined in the esterification process to form ethyl acetate and water. The term fat (or vegetable or animal oil) is confined to esters of a variety of long chain saturated or unsaturated fatty acids with glycerine (glycerides). Oils, cited in the prior art as vehicles for preparing putty-like materials, are exclusively glycerides, e.g., castor oil, sesame oil, olive oil, etc., as well as simple fatty acid esters such as ethyl laurate. What never have been proposed in the prior art as vehicles for preparing putty-like substances, are free liquid fatty carboxylic acids such as the saturated caprylic acid and the unsaturated oleic acid. Most important, the use of esters of fatty alcohols with low molecular weight mono- or polycarboxylic acids, e.g., lauryl acetate (the ester of lauryl alcohol and acetic acid) are completely novel for the preparation of putty-like materials and are chemically distinct from the prior art cited ethyl laurate (the ester of lauric acid with ethyl alcohol).

[0042] Returning now to the description of the Components of the present invention, more particularly Component 2, the elements are more specifically described as follows:

Materials useful as Component 2 are selected from a member of the group consisting of polyhydroxy compounds, polyhydroxy compound esters, solutions of polyhydroxy compound, and mixtures thereof.

[0043] Preferred among these are the liquid polyhydroxy compounds selected from the group consisting of acyclic polyhydric alcohols, polyalkylene glycols, and mixtures thereof. Specific examples of the foregoing are ethylene glycol, diethylene glycol, triethylene glycol, 1,2-propanediol, trimethylolethane, trimethylolpropane, erythritol, pentaerythritol or polyethylene glycols.

[0044] It should be noted that the foregoing polyhydroxy compounds may also be used, if desired, as Component 3 absorption accelerants. If DBM powder is present in the formulation then the polyhydroxy compound may not be an acyclic polyhydric alcohol, nonreducing sugar, sugar alcohol, sugar acid, monosaccharide, disaccharide, water-soluble or water dispersible oligosaccharide, polysaccharide, polyalkylene glycol or mixtures thereof.

[0045] As a statement of general applicability, it should be noted that Component 2 materials which are liquid at room temperature are the preferred substances for Component 2, and since they are liquids, a liquefying agent is not necessary. Also useful as Component 2 substances, however, are compounds which are solid at room temperature. In such cases, especially when putties are desired, a solid Component 2 is converted to a liquid form before, during, or after admixture with Component 1 through the use of an absorbable biocompatible liquefying agent capable of liquefying, solubilizing a solid Component 2. By "liquefying agent" as used herein, is meant an agent, such as a suitable solvent, which can solubilize the solid, or any other agent even though the agent may not be considered a solvent in the usual sense of that term, or an agent which can liquefy the solid, such as heat, or which can disperse the solid in a liquid as a dispersion so as to aid in the formation of a homogenous putty, cream or paste-like mixture. The particular agent used will, of course, depend upon the nature of Component 2 used in the particular formulation. Suitable agents are materials similar to Component 2 though not precisely described herein as Component 2.

[0046] The foregoing novel concepts and compositions utilizing the esters of monoalcohols with the mono- or polycarboxylic acids described above, provide an absorbable bone hemostatic implant. The novel utilization of relatively low molecular weight, non-toxic and rapidly degradable simple esters have been found to provide superior alternatives to the much higher molecular weight fatty acid triglycerides, e.g., castor oil, for Component 2. This aspect of the invention thus permits one to eliminate, if desired, both the art-known version of Component 2, i.e. hydrophobic, slowly absorbed esters such as the triglycerides typified by the ricinoleic acid triglyceride, castor oil, as well as by fatty acid esters such as isopropyl myristate and the need for the use of an absorption acceler-

ant.

[0047] These art-known putty compositions containing the art-known Component 2 materials, such as those of U.S. Patent 4,439,420 can, however, be used to obtain useful osteogenic bone hemostatic materials in accordance with another aspect described herein. It has been discovered that, when it is desired to have a bone hemostatic composition having osteogenic properties albeit with slower absorption characteristics, the art-known composition may be improved by the addition of osteogenic materials, e.g., demineralized bone matrix (DBM), mineralized bone matrix (MBM), hydroxyapatite, or growth factors such as bone morphogenic protein (BMP) and platelet derived growth factor (PDGF), as will described below.

Component 3- Optional

[0048] The third component, usually a hydrophilic material, is optionally included as an absorption accelerant and may even be used to control the kinetics of absorption by physically assisting in the disintegration of the implanted mass. Accelerants used in the prior art may be used if they are not toxic or otherwise bioincompatible. One or a combination of such prior art compounds as Carbowax®, the Pluronics®, (See discussion under Component 2 supra and discussion below) and glycerine, propylene glycol, lecithin, betaine, and polyhydroxy compounds such as hyaluronic acid, carboxymethylcellulose and chitosan and its acetyl derivatives may be used as absorption enhancers in the compositions of the invention, with the above caveat. It is preferred, however, to use for this purpose, other materials which are swellable or soluble and absorbable, such as either soluble or insoluble, natural or synthetic polypeptides, exemplified by purified, powdered insoluble fibrillar, but swellable collagens, the more rapidly absorbable soluble tropocollagens such as Vitrogen® and the more rapidly absorbable cold and hot water soluble polypeptides, e.g. the gelatins. Lecithin and octylphenyl ethoxylates, such as Triton® X 100, may be used as biocompatible surfactants to aid in swellability. Polyvinylpyrrolidone and other soluble, absorbable polymers such as the block copolymers of ethylene oxide and propylene oxide discussed supra in connection with Component 2, and relatively hydrophilic polypeptides, e.g., polyaspartic acid, polyglutamic acid, and their salts are also functional in this context. Most preferably, the compositions of the present invention contain, as the third component, insoluble, fibrillar collagen, soluble collagen, gelatin, octylphenyl ethoxylates (e.g. Triton® X 100), the block copolymers of ethylene oxide and propylene oxide, polyvinylpyrrolidone or absorbable phosphorus pentoxide-based glasses or stable mixtures of the foregoing. Particle sizes in the range of about 200-500 microns produce suitable results although larger or smaller particle sizes may be employed depending on the desires of the end user. Gelatin, PVP and other polymers have been used in the demineralized bone art as thickening additives but not as absorption accelerants. The thickening properties of gelatin vary directly with the Bloom number of the gelatin. Gelatin having Bloom numbers ranging from 100-300 are suitable in the compositions of the invention, although values above or below those numbers may be employed if the resulting product is acceptable to the end user.

[0049] Illustrative of some suitable proportions of Components which produce compositions having the properties described above, are the following:

Component 1. From about 5 to 80%, preferably about 20 to 50% by weight of the final composition.
Component 2. From about 10 to 70%, preferably about 20 to 50% by weight of the final composition.
Component 3. From about 0 to 80%, preferably about 10 to 70% by weight of the final composition.

[0050] While the foregoing discussion has been presented largely in the context of materials having the consistency of a putty, in some applications it may be desired to have a relatively less viscous or less cohesive composition. For example, it may be desired to place the composition of the invention into a void in the bone (drilled or otherwise formed, e.g. hairline fractures) into which a putty of high viscosity can be applied only with difficulty. A less viscous form of the putty compositions of the invention would be a desirable alternative. All one needs to do is modify the proportions presented herein to allow for a higher liquid concentration or add a compatible liquid diluent to achieve this purpose. Using this approach, an injectable form of the material can be obtained as well. Other less cohesive strength, non-putty compositions, such as creams, ointments, gels, lotions, and the like previously referred to, may be prepared in the same manner.

Component 4- Optional

[0051] The products described above are suitable hemostatic products which also will allow the growth of bone at the bone wound site. Thus, they are osteoconductive. A desirable aspect of the invention is to make the hemostatic product osteoinductive as well, that is, to provide the product with Component 4, a bone growth-inducing material (osteogenic material) in an amount effective to induce bone growth. Thus, it has been found that the inclusion of osteogenic materials such as growth factors, e.g. Platelet Derived Growth Factor (PDGF), Transforming Growth Factor beta (TGF-beta), Insulin-Related Growth Factor-I (IGF-I), Insulin-Related Growth Factor-II (IGF-II), Fibroblast Growth Factor (FGF), Beta-2-Microglobulin (BDGF II), bone morphogenic protein (BMP), and combinations thereof stimulate osteogenesis to varying degrees. Other bone growth-inducing materials such as demineralized bone matrix (DBM), osteonectin, osteocalcin, osteogenin, and combinations thereof, mineralized bone matrix (MBM), and/or hydroxyapatite, a

component of normal bone, as well as bioactive glasses, render the hemostatic product suitably osteogenic. Hydroxyapatite is an inorganic calcium phosphate mineral, prepared, among other ways, synthetically or from sea coral (from which all organic material has been removed), which has been demonstrated to support the rapid ingrowth of new bone tissue. Bioactive glasses are finely powdered glass particles which are biocompatible. They are useful as bone implant materials. A line of bioglasses is available commercially as VITRYXX™ from Schott, GmbH, Mainz, Germany. According to the manufacturer, when implanted into the body, the surface remodels to form "hydroxy carbono-apatite" upon which bone repair cells are deposited and form new bone tissue.

[0052] When used, a suitable amount of osteogenic material to be added to the compositions of the present invention ranges from about 0.001 to about 60% depending upon the material and preferably about 0.001 to about 40% by weight. When used as Component 4, i.e., as an osteogenic material, it is preferred to use certain agents such as DBM or mineralized bone in the form of larger average particle sizes. Suitable larger average particle sizes are in the range of about 0.05 to 10 mm preferably about 0.1 to 5 mm and most preferably about 0.5 to 1 mm. However, the use of Component 4 in smaller or larger particle sizes or in higher or lower amounts will also be suitable if the requirements of the ultimate user are satisfied.

[0053] With regard to the relative amounts of osteogenic material to be used in a composition of the invention, one would use a bone growth-inducing effective amount, by which is meant material adequate in amount and average particle size to be osteoinductive in the composition. The amount used may vary depending upon the efficacy of the osteogenic agent and the average particle size of the material. For example, growth factors such as BMP, Platelet Derived Growth Factor (PDGF) and the like are effective in fractional weight percent concentrations, whereas effective amounts of DBM, mineralized bone matrix, and hydroxyapatite are usually in higher weight percent concentrations, e.g., about 10% to about 50% or higher, and preferably in somewhat larger average particle sizes than those used in Component 1.

[0054] The addition of the bone growth-inducing material improves not only the compositions of the invention, but also improves the prior art hemostatic formulations to yield novel compositions therewith. Such additions will render these hemostatic formulations osteogenic as well. It is believed that the presence of the osteogenic material will also improve osteoconductive properties because the relatively large particles tend to "open up" the putty structure, thus providing spaces into which induced bone may proliferate.

[0055] The type of prior art hemostatic formulations which will especially be improved by such addition are the ones disclosed in U.S. Patents, 4,439,420 and 4,568,536.

Other Optional Ingredients

[0056] To any of the compositions described supra, may be added a pharmaceutically effective amount of an anti-infective agent, either alone or bound to a substrate to slow its release. Illustrative of such anti-infective materials are tetracycline, vancomycin, cephalosporins, and aminoglycosides such as tobramycin and gentamicin, alone or bound to collagen, for example, and combinations of the foregoing, iodine, alone or as a PVP complex, colloidal silver, silver salts, alone or bound to a carrier such as gelatin, collagen, and the like.

[0057] Other materials, such as a blood clot-inducing agents, e.g., epinephrine, tannic acid, ferrous sulfate, and the double-sulfates of a trivalent metal and a univalent metal such as potassium aluminum sulfate and ammonium aluminum sulfate; anti-neoplastic agents such as methotrexate, cis-platinum, doxorubicin, and combinations thereof, radionuclides such as Strontium 89, and the like; analgesics such as benzocaine, lidocaine, tetracaine, fentanyl (a potent non-opioid), and the like, anti-inflammatory substances such as the non-specific ibuprofen and aspirin, or the COX-2 specific inhibitors such as rofecoxib and celeboxib; radiopaque substances such as iodo, compounds, e.g., ethyl monoiodo stearate available as Ethiodol® (Savage Laboratories), and barium salts such as barium stearate, may be added in to the formulations in amounts which are effective to achieve their therapeutic or diagnostic purposes. Depending upon the characteristics of the colorant selected, colorants such as gentian violet, D&C Violet #2, and D&C Green #6 are suitable.

[0058] In some embodiments of the invention, it maybe desirable to intimately admix water with the compositions of the invention. The presence of a small amount of water, of the order of up to ten percent or more, aids in a variety of ways among which is changing the tactile quality of the composition. In this regard, the resulting compositions often impart a sensation of reduced coarseness over what may have existed in the compositions without the water addition. In some instances, it is desirable to provide a putty-like formulation or a less dense non-putty formulation having a cohesive strength less than that of a putty, such as a cream, a paste, or other such materials as previously set forth herein, based upon water or other aqueous liquids rather than on more hydrophobic vehicles. Bulking agents such as the metal fatty acid salts, e.g., calcium stearate and other non-wettable bulking agents described herein, are not wetted by water and do not provide putty-like (or less dense) compositions with water. We have found, however, that the treatment of the bulking agent with a small amount of surface-active material, e.g., lecithin, the Pluronics® such as Pluronic L-35®, renders the unwettable bulking agent sufficiently wettable to enable the preparation of a suitable fatty acid salt-water formulation when Component 2 is an aqueous vehicle. Suitable aqueous vehicles are water, saline, various biocompatible buffer solutions, various body fluids,

such as blood, serum, blood component concentrates, and the like.

[0059] While the above putties have less resistance to irrigation compared with the putties prepared using more hydrophobic materials, they have applications in bone defect repair where more rapid disintegration of the implant is desired. Non-ionic, cationic, and anionic surfactants are suitable, although virtually any biocompatible surfactant may be used as exemplified by dodecyl trimethyl ammonium chloride, sodium lauryl sulfate, nonoxynol-9, the Tweens, e.g., polyoxyethylenesorbitan monolaurate, Tergitol-7, i.e., sodium heptadecyl sulfate, and the antimicrobial surfactant, 1-lauryl-3-ethylbehzotriazolium bromide, and the like. Non-putty-like compositions, such as creams, pastes, and the like, may be prepared by using additional quantities of water. This is especially useful during surgical procedures when it is desired to form a putty- or cream-like composition using blood instead of water.

[0060] The foregoing discussion relating to the use of blood clot-inducing agents in the present invention illustrates the embodiment wherein the compositions are capable of chemical hemostasis in use. That is, the addition of the styptic material to the compositions of the present invention, whether those compositions are mechanically hemostatic or not, yields compositions having the ability to act as chemical hemostatic materials. Thus, an already mechanically hemostatic putty can be made more efficiently hemostatic by adding the blood clot-inducing material. Similarly, a lower cohesive strength cream or paste, which may lack significant mechanical hemostatic properties, can be made hemostatic by the addition of the blood clotting material. An example of the latter is the application of a thin layer of a vasoconstrictor-modified paste of the invention to a bleeding acetabulum in hip surgery.

[0061] The components described above, when added together in suitable proportions, yield useful, putty-like and non-putty like agents having, to varying degrees, many favorable characteristics. Various combinations of the components may require different times and temperatures in the preparation process in order for the putty-like characteristics to develop. For example, some materials such as finely divided hydroxyapatite may take longer than other components to achieve the putty-like state. In general, the putty-like compositions of the present invention are absorbable within a reasonable time, usually within 30 days although absorption times may be extended to several months or longer for some applications. They are moldable and shapeable by hand at ambient temperatures, handle well in presence of blood, and are washable with saline. They sometimes are tacky to the touch, but do not stick to any great degree to surgical gloves, wet or dry. They can be radiation sterilized when radiation-sensitive material such as DBM or certain antibiotics are not present.

[0062] The actual proportions of the materials selected will vary depending upon the materials themselves, the number of components used, and the use desired for the final putty composition. The user will be guided initially by the requirement for the desired viscosity, cohesive strength, and consistency to be obtained, i.e. compositions ranging from flowable liquid consistencies to consistencies of creams, pastes, ointments, gels, and the like to the more cohesive putty-like consistencies, while maintaining other characteristics desired in the ultimate use of the component.

[0063] The compositions described in this specification, when used surgically, must be sterile. All, except those noted below, are radiation sterilizable using, for example, a standard cobalt-60 radiation source and a nominal dose of 25 kGy. Exceptions are formulations containing radiation-sensitive additives such as demineralized bone matrix, bone morphogenic protein, certain antibiotics, unsaturated molecules such as oleic acid and the like. When such materials are used, sterility may be achieved by radiation-sterilizing the bulk putty-like material and aseptically adding the sterile radiation-sensitive additive followed by aseptic packaging.

[0064] The compositions described in this specification may be sterile or sterilizable and may be packaged in several formats. The packages themselves may be sterile or sterilizable. The compositions may be packaged as an amorphous (i.e., shapeless or having no definite shape) material such as a paste, cream, or putty, or in the shape of its container. They may be shaped generally as a parallelepiped or as a generally rounded form, examples of the former being small brick-shapes or slabs (in the shape of a stick of chewing gum), and examples of the latter being cylindrical-shaped, egg-shaped, or spherical-shaped products. Alternatively, when the application permits and the viscosity is suitable, the product can be packaged in a syringe-like or plunger-assisted dispenser expressable or extrudable through an orifice of appropriate cross section and shape. A mechanical assist device similar to that used for caulking may be included. Another package contains the product in a squeezable, deformable tube such as a toothpaste-type tube or a collapsible tube such as those used in caulking . applications, with an orifice shaped and sized to dispense any suitable shape onto the surface to be treated. The package may comprise an outer barrier as an overwrap, for example, a peelable blister pouch, to allow aseptic delivery of the package to the sterile field.

[0065] The present invention also contemplates methods of use of the compositions of the invention. For example, one embodiment is the method of mechanically controlling the bleeding of bone by the application of an effective amount of any of the compositions of the invention to bleeding bone, wherein the composition has a sufficiently dense consistency, such as in the putty compositions of the invention. In such a case, the composition is a mechanical hemostatic tamponade.

[0066] Another embodiment of the method of use of the invention is the method of chemically controlling the bleeding of bone by the application of an effective amount

of any of the compositions of the invention, wherein the composition contains a blood clot-inducing agent as heretofore set forth. In the case of putties, the composition is a chemical hemostatic tamponade. Mechanical hemostatic tamponades of the invention which also comprise a clot-inducing agent will act as both a mechanical hemostat and a chemical hemostat.

[0067] Another method of the invention is the method for inducing the growth of bone in a bone defect by applying an effective amount of any composition of the invention containing a bone growth-inducing agent, to the affected area of bone, especially when the composition includes a bone growth-inducing material such as DBM, mineralized bone matrix, bone morphogenic protein, hydroxyapatite, or the like.

[0068] Another method is the method for treating an infection in or around a bone by applying an effective amount of any composition of the invention containing an anti-infective agent, to the affected area of bone to be treated.

[0069] Another method is the method for destroying cancer cells in or around a bone by applying an effective amount of any composition of the invention containing an anti-neoplastic agent, to the affected area of bone which contains such cells.

[0070] Another method is the method for reducing pain from an area in or around a bone by applying an effective amount of any composition of the invention containing an analgesic agent, to the affected area.

[0071] Another method is the method for controlling inflammation in or around a bone by applying an effective amount of any composition of the invention containing an anti-inflammatory agent, to the affected area.

[0072] Another method is the method for assessing the status of an area in bone to which an implant has been applied by applying an effective amount of any composition of the invention containing a radiopaque agent, to the affected area and thereafter radiographically visualizing the area and making a determination of the status of the area.

[0073] Another method is the method for rendering wettable any of the bulking agents used in the invention which may be hydrophobic by treating the bulking agent with a cationic, anionic, or non-ionic surfactant and then making a water-based putty from the treated bulking agent using any source of liquid such as water itself, saline, or body fluids such as blood, serum, or the like.

[0074] Those skilled in the art will be aware of the manner in which the compositions are applied and the amount thereof. In some applications, large amounts of the tamponade may be used while in others only small amounts may be required or desired.

Claims

1. A body-absorbable composition comprising in intimate admixture Components 1 and 2, wherein Component 1 is a finely powdered carboxylic acid salt comprising a carboxylate anion and a metallic cation, wherein said carboxylic acid is carboxymethyl cellulose and wherein the average particle size of component 1 is 50 microns or less, and Component 2 is a liquid comprising a member selected from the group consisting of polyhydroxy compounds, polyhydroxy compound esters and polyhydroxy compound ethers, and mixtures of the foregoing.

2. The composition of claim 1, wherein Component 1 is 5-80% by weight of the final composition, and Component 2 is 10-70% by weight of the final composition.

3. The composition of any one of claims 1-2, wherein the polyhydroxy compound of Component 2 comprises glycerol, glyceryl monoesters, glyceryl diesters, glyceryl triesters, glyceryl monoethers, glyceryl diethers, or glyceryl triethers, preferably selected from diethylene glycol, triethylene glycol, 1,2-propanediol, trimethylolethane, trimethylolpropane, erythritol, pentaerythritol, or a polyethylene glycol.

4. The composition of any one of claims 1-3, further comprising an optional Component 3 comprising absorbable soluble or insoluble, natural or synthetic peptides, insoluble fibrillar collagens, soluble tropocollagen, gelatin, lecithin, betaine, octylphenyl ethoxylates, polyvinylpyrrolidone, absorbable phosphorous pentoxide-based glasses, or a block copolymer of ethylene oxide and propylene oxide.

5. The composition of claim 4, wherein Compound 3 comprises gelatin, octylphenyl ethoxylates, or a block copolymer of ethylene oxide and propylene oxide.

6. The composition of any one of claims 1-5, further comprising a Component 4 comprising growth factors, demineralized bone matrix (DBM), mineralized bone matrix, hydroxyapatite, or bone morphogenic protein in bone growth-inducing amounts, preferably selected from hydroxyapatite or DBM.

7. The composition of any one of claims 1-6, wherein the composition is sterile or sterilizable.

8. The composition of any one of claims 1-7, further comprising an anti-infective agent or a colorant, or both.

9. A package comprising the composition of any one of claims 1-8.

10. The package of claim 9, wherein the package is sterile or sterilizable.

11. The package of claim 9, wherein the composition is in an amorphous form or in a generally rounded form, or in a generally parallelepiped form.

12. The package of claim 9, wherein the package comprises a syringe-like or plunger-assisted dispenser.

13. The package of claim 9, wherein the package comprises a squeezable, deformable tube.

14. The package of claim 9, wherein the package comprises an outer barrier as an overwrap to allow aseptic delivery of the package into a sterile field.

15. The composition of any one of claims 1-8 for use in mechanically controlling the bleeding of bone.

Patentansprüche

1. Vom Körper absorbierbare Zusammensetzung, die Komponenten 1 und 2 in inniger Mischung umfasst, wobei Komponente 1 ein feinpulvriges Carbonsäurensalz ist, das ein Carboxylatanion und ein Metallkation umfasst, wobei die Carbonsäure Carboxymethylcellulose ist und wobei die durchschnittliche Teilchengröße von Komponente 1 50 Mikron oder weniger ist, und Komponente 2 eine Flüssigkeit ist, die ein Element umfasst, das aus der Gruppe bestehend aus Polyhydroxyverbindungen, Polyhydroxyverbindungsestern und Polyhydroxyverbindungsethern und Gemischen der vorstehenden ausgewählt ist.

2. Zusammensetzung nach Anspruch 1, wobei Komponente 1 5-80 Gew.-% der Endzusammensetzung ausmacht und Komponente 2 10-70 Gew.-% der Endzusammensetzung ausmacht.

3. Zusammensetzung nach einem der Ansprüche 1-2, wobei die Polyhydroxyverbindung von Komponente 2 Glycerin, Glycerylmonoester, Glyceryldiester, Glyceryltriester, Glycerylmonoether, Glyceryldiether oder Glyceryltriether umfasst, vorzugsweise aus Diethylenglykol, Triethylenglykol, 1,2-Propandiol, Trimethylolethan, Trimethylolpropan, Erythrit, Pentaerythrit oder einem Polyethylenglykol ausgewählt ist.

4. Zusammensetzung nach einem der Ansprüche 1-3, die weiterhin eine optionale Komponente 3 umfasst, die absorbierbare lösliche oder unlösliche, natürliche oder synthetische Peptide, unlösliche fibrilläre Kollagene, lösliches Tropokollagen, Gelatine, Lecithin, Betain, Octylphenylethoxylate, Polyvinylpyrrolidon, absorbierbare Gläser auf Phosphorpentoxid-Basis oder ein Blockcopolymer von Ethylenoxid und Propylenoxid umfasst.

5. Zusammensetzung nach Anspruch 4, wobei Verbindung 3 Gelatine, Octylphenylethoxylate oder ein Blockcopolymer von Ethylenoxid und Propylenoxid umfasst.

6. Zusammensetzung nach einem der Ansprüche 1-5, die weiterhin eine Komponente 4 umfasst, die Wachstumsfaktoren, entmineralisierte Knochenmatrix (DBM), mineralisierte Knochenmatrix, Hydroxyapatit oder knochenmorphogenetisches Protein in das Knochenwachstum induzierenden Mengen umfasst, vorzugsweise aus Hydroxyapatit oder DBM ausgewählt ist.

7. Zusammensetzung nach einem der Ansprüche 1-6, wobei die Zusammensetzung steril oder sterilisierbar ist.

8. Zusammensetzung nach einem der Ansprüche 1-7, die weiterhin ein Antiinfektivum oder einen Farbstoff oder beides umfasst.

9. Packung, die die Zusammensetzung nach einem der Ansprüche 1-8 umfasst.

10. Packung nach Anspruch 9, wobei die Packung steril oder sterilisierbar ist.

11. Packung nach Anspruch 9, wobei die Zusammensetzung in einer amorphen Form oder in einer allgemein abgerundeten Form oder in einer allgemeinen Parallelepipedform ist.

12. Packung nach Anspruch 9, wobei die Packung eine spritzenartige oder kolbengestützte Abgabevorrichtung umfasst.

13. Packung nach Anspruch 9, wobei die Packung ein quetschbares, verformbares Röhrchen umfasst.

14. Packung nach Anspruch 9, wobei die Packung eine Außenbarriere als eine Außenverpackung umfasst, um eine aseptische Überführung der Packung in einen Sterilbereich zu ermöglichen.

15. Zusammensetzung nach einem der Ansprüche 1-8 zur Verwendung beim mechanischen Regulieren des Blutens von Knochen.

Revendications

1. Composition absorbable par le corps comprenant un mélange intime de composants 1 et 2, dans laquelle le composant 1 est un sel d'acide carboxylique finement pulvérisé comprenant un anion carboxylate et un cation métallique, ledit acide carboxylique étant la carboxyméthylcellulose et la taille moyenne des particules du composant 1 étant inférieure ou égale

à 50 micromètres, et le composant 2 est un liquide comprenant un élément choisi dans le groupe constitué par les composés polyhydroxylés, les esters de composés polyhydroxylés et les éthers de composés polyhydroxylés et les mélanges des éléments susdits.

2. Composition selon la revendication 1, dans laquelle le composant 1 représente 5-80 % en poids de la composition finale et le composant 2 représente 10-70 % en poids de la composition finale.

3. Composition selon l'une quelconque des revendications 1-2, dans laquelle le composé polyhydroxylé du composant 2 comprend du glycérol, des monoesters de glycéryle, des diesters de glycéryle, des triesters de glycéryle, des monoéthers de glycéryle, des diéthers de glycéryle ou des triéthers de glycéryle, de préférence choisi entre le diéthylèneglycol, le triéthylèneglycol, le propane-1,2-diol, le triméthylolléthane, le triméthylolpropane, l'érythritol, le pentaérythritol ou un polyéthylèneglycol.

4. Composition selon l'une quelconque des revendications 1-3, comprenant en outre un composant 3 facultatif comprenant des peptides naturels ou synthétiques solubles ou insolubles absorbables, des collagènes fibrillaires insolubles, du tropocollagène soluble, de la gélatine, de la lécithine, de la bétaïne, des produits d'éthoxylation octylphényliques, de la polyvinylpyrrolidone, des verres à base de pentoxyde de phosphore absorbables ou un copolymère séquencé d'oxyde d'éthylène et d'oxyde de propylène.

5. Composition selon la revendication 4, dans laquelle le composé 3 comprend de la gélatine, des produits d'éthoxylation octylphényliques ou un copolymère séquencé d'oxyde d'éthylène et d'oxyde de propylène.

6. Composition selon l'une quelconque des revendications 1-5, comprenant en outre un composant 4 comprenant des facteurs de croissance, de la matrice osseuse déminéralisée (DBM), de la matrice osseuse minéralisée, de l'hydroxyapatite ou une protéine morphogénétique osseuse en quantités induisant la croissance osseuse, de préférence choisi entre l'hydroxyapatite et la DBM.

7. Composition selon l'une quelconque des revendications 1-6, la composition étant stérile ou stérilisable.

8. Composition selon l'une quelconque des revendications 1-7, comprenant en outre un agent anti-infectieux ou un colorant ou les deux.

9. Conditionnement comprenant la composition selon l'une quelconque des revendications 1-8.

10. Conditionnement selon la revendication 9, le conditionnement étant stérile ou stérilisable.

11. Conditionnement selon la revendication 9, dans lequel la composition est sous une forme amorphe ou sous une forme généralement arrondie ou sous une forme généralement parallélépipédique.

12. Conditionnement selon la revendication 9, le conditionnement comprenant un distributeur de type seringue ou assisté par piston.

13. Conditionnement selon la revendication 9, le conditionnement comprenant un tube déformable pressable.

14. Conditionnement selon la revendication 9, le conditionnement comprenant une barrière extérieure en tant que suremballage pour permettre la pose aseptique du conditionnement dans un champ stérile.

15. Composition selon l'une quelconque des revendications 1-8 destinée à être utilisée pour juguler mécaniquement le saignement d'un os.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- GB 1584080 A **[0011]**
- US 6117444 A **[0011]**
- US 6454787 B **[0011]**
- US 4186448 A **[0011]**
- US 5143730 A **[0011]**
- US 6420454 B **[0011]**
- US 5641502 A **[0011]**
- US 6413539 B **[0011]**
- US 4443430 A **[0011]**
- US 6485749 B **[0011]**
- US 4568536 A **[0012] [0015] [0055]**
- US 4439420 A **[0012] [0015] [0016] [0047] [0055]**
- US 4650665 A **[0012]**
- US 5073373 A **[0013]**
- US 5484601 A **[0013]**
- US 5284655 A **[0013]**
- US 5290558 A **[0013]**
- US 5314476 A **[0013]**
- US 6030635 A **[0013]**
- US 6437018 B **[0013]**
- US 6565884 B **[0014]**
- US 6576249 B **[0014]**